

**REMARKS**

Favorable consideration of the subject application, in light of the following remarks, are respectfully requested.

The Examiner has required Applicants to make two separate elections based upon the alleged lack of unity of invention in the present national stage application.

In response, Applicants hereby elect, with traverse:

- **Group (a)**, claims 1-14, characterized by the Examiner as being drawn to an isolated nucleic acid molecule comprising SEQ ID NO: 1, the complement of said sequence, sequences having at least 80% identity to said sequence and nucleotide sequences which hybridize to said sequence; and further wherein said nucleic acid molecules are used as a marker for determining the differentiation of human stem cells; and
- the single nucleic acid molecule of **Group (1)**, SEQ ID NO: 84.

Applicants respectfully request that the Examiner reconsider the particular invention groupings since Groups (a)-(f), and similarly Groups 1-4, are linked so as to form a single general inventive concept.

Group (a), which Applicants have elected, comprises SEQ ID NO:1, which as indicated in Table 1 of the specification is identified as miR-302b\*. SEQ ID NOS: 2-6 are identified as miR-302b, miR-302c\*, miR-302c, miR-302a\*, and miR-302d, respectively. See Specification at 6-7, Table 1. SEQ ID NO: 84, the single nucleic acid molecule that Applicants have elected, is the precursor for miR-302b\* and miR-302b. SEQ ID NOS: 85-87 are the precursors for miR-302c\* and miR-302c; miR-302a\* and miR-302a; and miR-302d, respectively. See Paper Copy of Sequence Listing.

Each of miR-302a, miR-302b, miR-302c, and miR-302d are isolated from human embryonic stem cell and clustered in human chromosome IV. The cluster of rniR-302a, miR-302b, miR-302c, and miR-302d can be used for determination of stem cell type, for distinguishing between human embryonic stem cells and mouse embryonic stem cells, and for selecting human embryonic stem cells or human embryonic carcinoma stem cells. See Specification at 16 (line 7) - 17 (line 9)..

The clustering of miR-302a, miR-302b, miR-302c and miR-302d is also disclosed in the referenced miRNA database (<http://micromir.sanger.ac.uk>). The database discloses 21 miRNA as a mir-302 gene family (see enclosed Reference 1 ([http://microrna.sanger.ac.uk/cgi-bin/sequences/mirna\\_summary.pl?fam=MIPF000071](http://microrna.sanger.ac.uk/cgi-bin/sequences/mirna_summary.pl?fam=MIPF000071))). Among the mir-302 gene family, hsa-mir302a, hsa-mir302b, hsa-mir302c and hsa-mir302d correspond miR-302a, miR-302b, miR-302c, miR-302d, respectively (see enclosed References 2 to 5, the stem loop structures of References 2 to 5 are the same as the structure of Fig 1 of the present invention, respectively.)

Moreover, nucleotides of SEQ ID NO:1 to 6 have high sequence homology (78%) to each other. (In Reference 6, panel A is the result of analyzing the sequence homology of precursor of siRNA of the present invention; and panel B is the result of analyzing the sequence homology of siRNA of the present invention).

Therefore, nucleotides of SEQ 1D NO:1-6 are members of the miR-302 gene family (and SEQ ID NO: 84-87 as precursors). As such Groups (a)-(f) and Groups 1-4 are linked so as to form a general inventive concept and thus possess unity of invention. In view of the foregoing, the examiner is respectfully requested to

combine Groups (b)-(f) with already elected Group (a), and to combine Group 2-4 with already elected Group 1.

Applicants response is made without prejudice or disclaimer to any non-elected subject matter, and Applicants reserve the right to file one or more continuation and/or divisional applications directed to any non-elected subject matter.

In view of the foregoing, further favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

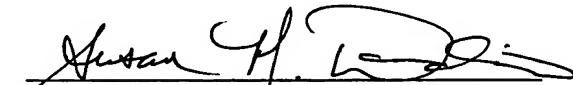
In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 18, 2008

By:

  
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Alexandria, VA 22313-1404  
703 836 6620



# miRBase::Sequences

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## miRNA gene family: mir-302 (21 sequences)

ID	Accession	Chromosome	Start	End	Strand	Fetch
oza-mir-302a	MI0001241	4	58651879	58651945	-	[F]
oza-mir-302b	MI0003700	4	58651914	58651985	-	[F]
oza-mir-302c	MI0003701	4	58651576	58651640	-	[F]
oza-mir-302d	MI0003702	4	58652214	58652282	-	[F]
hsa-mir-302a	MI0000738	4	113788788	113788856	-	[F]
hsa-mir-302a	MI0000772	4	113789090	113789162	-	[F]
hsa-mir-302c	MI0000773	4	113788968	113789035	-	[F]
hsa-mir-302e	MI0000774	4	113788609	113788676	-	[F]
rdo-mir-302a	MI0005373	5	66074649	66074718	-	[F]
rdo-mir-302b	MI0005374	5	66075008	66075078	-	[F]
rdo-mir-302c	MI0005372	5	66074864	66074922	-	[F]
rdo-mir-302d	MI0005374	5	66074483	66074556	-	[F]
mmu-mir-302a	MI0007687	5	105472356	105472424	-	[F]
mmu-mir-302b	MI0007688	5	105472668	105472743	-	[F]
mmu-mir-302c	MI0007689	5	105472533	105472600	-	[F]
mmu-mir-302d	MI0007690	5	105472190	105472257	-	[F]
mmu-mir-302a	MI0000402	3	127248444	127248482	-	[F]
mmu-mir-302b	MI0003716	3	127248146	127248219	-	[F]
mmu-mir-302c	MI0003717	3	127248281	127248348	-	[F]
mmu-mir-302d	MI0003718	3	127248542	127248607	-	[F]
xtr-mir-302	MI0004878	scf001489	1068787	1068855	-	[F]

Get selected sequences:

Stem-loop sequence 

Select sequences and output type, then click "Fetch Sequences":  Unaligned fasta format 

miRNA gene family: mir-302 (21 sequences)

Comments or questions ? Send a mail to [microrna@sanger.ac.uk](mailto:microrna@sanger.ac.uk)



## miRNA Entry for MI0000738

Clustered miRNAs	miRNA	Database links
hsa-mir-302a	4-113789090-113789162	<a href="#">HGNC:31623</a> <a href="#">MIRN302A</a>
hsa-mir-302b	4-113788963-113789035	<a href="#">HGNC:31623</a> <a href="#">MIRN302B</a>
hsa-mir-302c	4-113788783-113788856	<a href="#">HGNC:31623</a> <a href="#">MIRN302C</a>
hsa-mir-302a	4-113788609-113788676	<a href="#">HGNC:31623</a> <a href="#">MIRN302A</a>
hsa-mir-302d	4-113788479-113788546	<a href="#">HGNC:31623</a> <a href="#">MIRN302D</a>
hsa-mir-302e	4-113788353-113788420	<a href="#">HGNC:31623</a> <a href="#">MIRN302E</a>
hsa-mir-302f	4-113788226-113788293	<a href="#">HGNC:31623</a> <a href="#">MIRN302F</a>
hsa-mir-302g	4-113788100-113788167	<a href="#">HGNC:31623</a> <a href="#">MIRN302G</a>

## Mature sequence MIMAT0000684

Minor miR\* sequence MIMAT0000683

Predicted  
targets

MIRANDA: hsa-miR-302a  
TARGETSCAN: hsa-miR-302a

## References

- 1 Embryonic stem cell specific microRNAs  
Houbaviy HB, Murray MF, Sharp PA  
*Dev Cell* 5:351-358 (2003)
- 2 Human embryonic stem cells express a unique set of microRNAs  
Sun MR, Lee Y, Kim Y, Kim SK, Moon SH, Lee JY, Cha KJ, Chung HM, Yooja HS, Moon SY, Kim VN, Kim KS  
*Dev Biol* 270:489-498 (2004)
- 3 New human and mouse microRNA genes found by homology search  
Weber MJ  
*FEBS J* 272:59-73 (2005)
- 4 A mammalian microRNA expression database based on small RNA library sequencing  
Landgraf P, Rusu M, Sheridan R, Seiver A, Iovino N, Aravin A, Preffer S, Rice A, Kammerstorfer A, Landthaler M, Lin C, Socci ND, Helmschmid C, Fulci V, Chiaretti S, Foa R, Schliwka T, Fuchs U, Novosel A, Müller PU, Schermer B, Bissels U, Inman J, Phan Q, Chien M  
*Cell* 129:1401-1411 (2007)

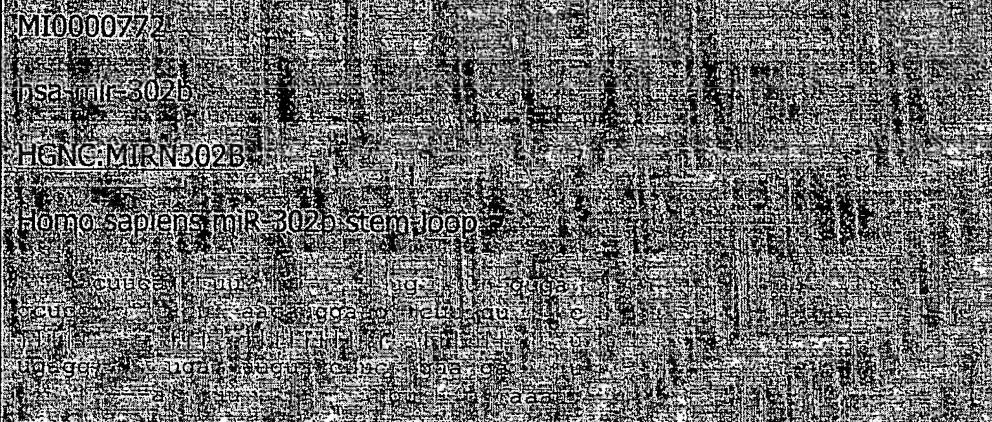
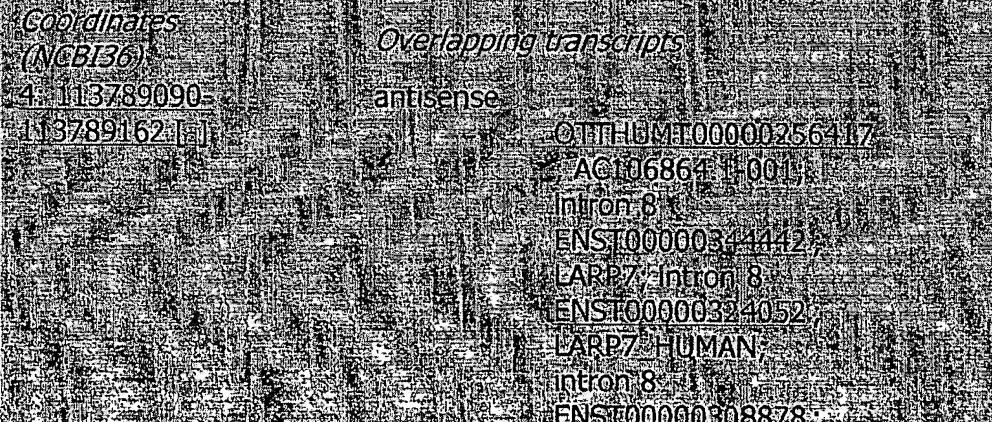
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# miRBase:Sequences

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## Stem-loop sequence MI0000772

<b>Accession</b>	MI0000772
<b>ID</b>	hsa-mir-302b
<b>Symbol</b>	HGNC:MIRN302b
<b>Description</b>	Homo sapiens miR-302b stem-loop
<b>Stem-loop</b>	
<b>Get sequence</b>	<a href="#">Get sequence</a>
<b>Comments</b>	Human miR-302a (MI0000738), miR-302b (MI0000772), miR-302c (MI0000739), miR-302d (MI0000740) and miR-307 (MI0000755) are clustered on chromosome 4. The mature sequence shown here represents the most commonly cloned form from large-scale cloning studies [2].
<b>Coordinates</b> (NCBI36)	4:113789090-113789162
<b>Genome context</b>	
<b>View flanking features</b>	<a href="#">View flanking features</a>
<b>OK from hsa-mir-302b</b>	<a href="#">OK from hsa-mir-302b</a>

## miRNA Entry for MI0000772

	hsa-mi-302b	4-113789090-113789162
Clustered miRNAs	hsa-mi-302c	4-113788968-113789055
	hsa-mi-302d	4-113788738-113788856
	hsa-mi-302d	4-113788609-113788676
	hsa-mi-367	4-113788479-113788546
Database links	HGNC: 81763   MIRN302B	
Gene family	MIPF0000074   mi-302	

## Mature sequence MIMAT0000715

## Minor miR\* sequence MIMAT0000714

<b>Accession</b>	MIMAT0000711
<b>ID</b>	hsa-mir-3025
<b>Sequence</b>	 32
	<a href="#">Get sequence</a>
<b>Evidence</b>	experimental (cloned), RT-21 (Northern blot)
<b>Predicted</b>	MIRANDA: hsa-mir-3025

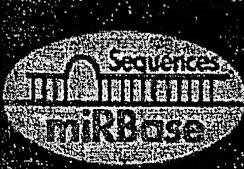
targets

TARGETSCAN Human R6025

## References

- 1 "Human embryonic stem cells express a unique set of microRNAs"  
Suh MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM, Yoon HS, Moon SY, Kim VN, Kim KS  
*Dev Biol* 270:488-498 (2004)
- 2 "A mammalian microRNA expression atlas based on small RNA library sequencing"  
Landgraf P, Rusu M, Sheridan R, Sewer A, Iovine N, Aravin A, Pfleiderer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chareau S, Ercsi R, Schluwke T, Fuchs U, Novosel A, Müller RU, Schermer B, Bissels U, Hummel J, Phan O, Chien M, Gaidatzis D, Reinert K, Stark A, Meister G  
*Cell* 129:1403-1414 (2007)

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# miRBase:Sequences

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## Stem-loop sequence MI0000773

Accession	MI0000773						
ID	hsa-mir-302c						
Symbol	HGNC: MIRN302C						
Description	Homo sapiens miR-302c stem-loop						
Stem-loop	 <a href="#">Get sequence</a>						
Coordinates (NCBI36)	4:113788968-113789035						
Genome context	<table border="1"><thead><tr><th>Overlapping transcripts</th></tr></thead><tbody><tr><td>antisense: OTTHUMT0000025647 AC105864-1-01 DEG8 ENST00000344412 LARP7/intron 8 ENST00000324052 LARP7/HUMAN IDR0006 ENST00000308378 Q4G0P3-2/intron 8</td></tr></tbody></table> <a href="#">View flanking features</a>  <a href="#">&lt; 10kb from hsa-mir-302c</a>  <table border="1"><thead><tr><th>Clustered miRNAs</th></tr></thead><tbody><tr><td>hsa-mir-302b</td></tr><tr><td>hsa-mir-302c</td></tr><tr><td>hsa-mir-302a</td></tr></tbody></table>	Overlapping transcripts	antisense: OTTHUMT0000025647 AC105864-1-01 DEG8 ENST00000344412 LARP7/intron 8 ENST00000324052 LARP7/HUMAN IDR0006 ENST00000308378 Q4G0P3-2/intron 8	Clustered miRNAs	hsa-mir-302b	hsa-mir-302c	hsa-mir-302a
Overlapping transcripts							
antisense: OTTHUMT0000025647 AC105864-1-01 DEG8 ENST00000344412 LARP7/intron 8 ENST00000324052 LARP7/HUMAN IDR0006 ENST00000308378 Q4G0P3-2/intron 8							
Clustered miRNAs							
hsa-mir-302b							
hsa-mir-302c							
hsa-mir-302a							

## miRNA Entry for MI0000773

<b>Database links</b>	<a href="#">HGNC-31764-MIRN302C</a>
<b>Gene family</b>	MIRF0000071-miR-302
	4: 113788609-113788676 [ <a href="#">View</a> ] [ <a href="#">Edit</a> ]

Mature sequence MIMAT0000717

Minor miR\* sequence MIMAT0000716

## References

[http://microrna.sanger.ac.uk/cgi-bin/sequences/mirna\\_entry.pl?acc=MI0000773](http://microrna.sanger.ac.uk/cgi-bin/sequences/mirna_entry.pl?acc=MI0000773)

miRNA Entry for MI0000773

1

Suh MR, Lee Y, Kim JY, Kim SK, Moon TSH, Lee MJ, Cha KY, Chung HM, Yoon HS, Moon SY, Kim VN, Kim KS  
*Dev Biol* 270:488-498 (2004)

2

"A mammalian microRNA expression atlas based on small RNA library sequencing"  
Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chiaretti S, Foa R, Schliwka J, Fuchs U, Novosel A, Müller RU, Schermer B, Bissels U, Irnman J, Phan Q, Chien M  
*Cell* 129:1401-1414 (2007)

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**Sequences**  
**miRBase**

# miRBase::Sequences

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## Stem-loop sequence MI0000774

<b>Accession</b>	MI0000774
<b>ID</b>	hsa-mir-302d
<b>Symbol</b>	HGNC:MIRN302D
<b>Description</b>	Homo sapiens miR-302d stem-loop
<b>Stem-loop</b>	 Get sequence
<b>Comments</b>	Human miR-302a (MI0000733), miR-302b (MI0000722), miR-302c (MI0000734), miR-302d (MI0000723) and miR-307 (MI0000735) are clustered on chromosome 4.
<b>Coordinates</b>	NCBI36
	4:113788609 -> 4:113788676 [+]
<b>Genome context</b>	<b>Overlapping transcripts</b> antisense: OTTHUMT00000256417 AC106864.1-001 Intron 3: ENST00000344442 LARP7: Intron 8: ENST00000324052 LARP7: HUMAN: Intron 8: ENST00000308878 Q4G0J3_2: intron 8: ENST00000308878
	<b>View flanking features</b>
	<- 10Kb from hsa-mir-302d
	hsa-mir-302d
	4:113789090 -> 4:113789162

## miRNA Entry for MI0000774

Gene family	MIPER0000071 - miR-302d	HGNC: 31765 - MIRN302D
Clustered miRNAs	hsa-mi-302c hsa-mi-302a hsa-mi-302d hsa-mi-367	hsa-mi-302c hsa-mi-302a hsa-mi-302d hsa-mi-367
Database links		

## Mature sequence MIMAT0000718

Minor miR\* sequence MIMAT0004685

Accession	MIMAT0001685
ID	hsa-miR-302d
Sequence	<a href="#">Get sequence</a>
Evidence	experimental [Gore et al.]
Predicted targets	MIRANDA: hsa-miR-302d TARGETSCAN: hsa-miR-302d

## References

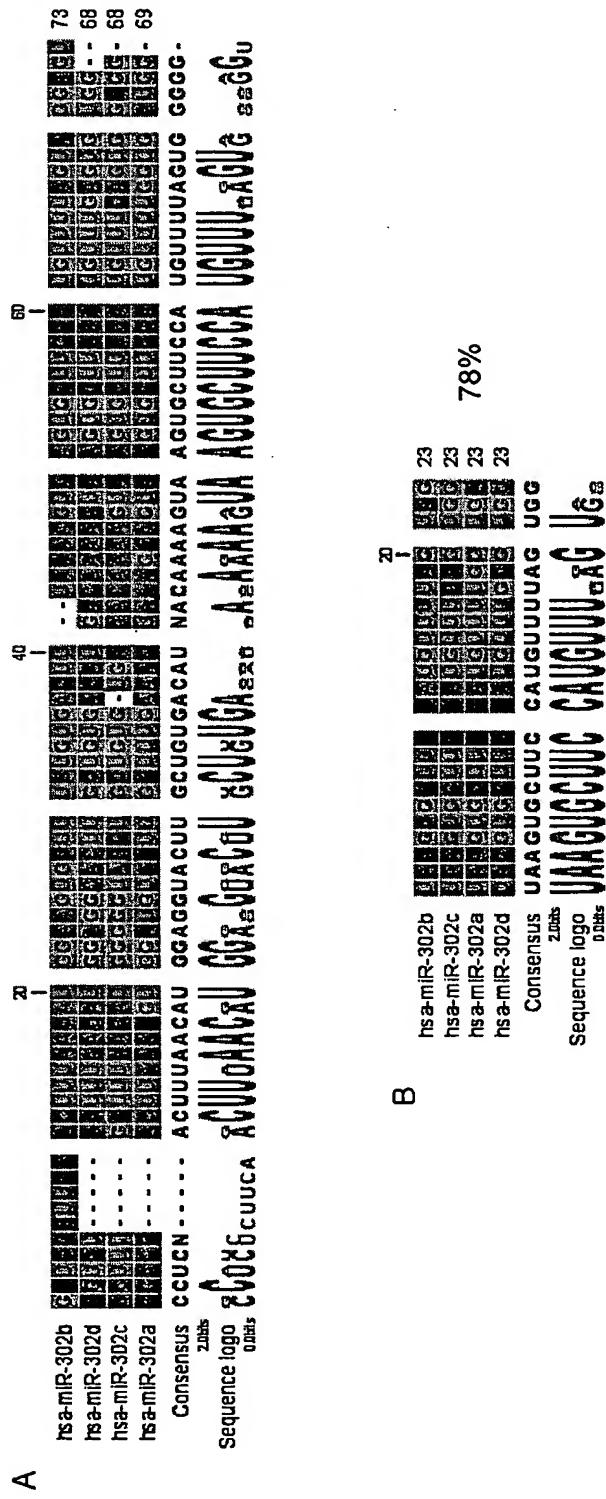
1

"Human embryonic stem cells express a unique set of microRNAs"  
Suh MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM,  
Yoon HS, Moon SY, Kim VN, Kim KS  
*Dev Biol.* 270:488-498(2004)

2

"A mammalian microRNA expression atlas based on small RNA library sequencing"  
Landgraf P, Rudi T, Sheridan R, Sewer A, Iovino N, Aravin A, Preffer S,  
Rice A, Kamphorst AO, Landthaler M, Lin G, Saito ND, Hermida L, Fulci V, Chiaretti S, Foa R, Schluwak J, Fuchs U, Novosel A, Müller RU,  
Scheiner B, Bissels U, Inman D, Phan O, Chien M  
*Cell* 129:1401-1414(2007)

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Alignment of miR-302b, miR-302c, miR-302a, and miR-302a from human genome sequence.

- A. Alignment of the precursor microRNAs from human miR-302b, miR-302c, miR-302a, and miR-302d.
- B. Alignment of the mature microRNAs from human miR-302b, miR-302c, miR-302a, and miR-302d.

Abbreviations: has, *Homo sapiens*.